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Clinical Implications of the New TSH Reference Range

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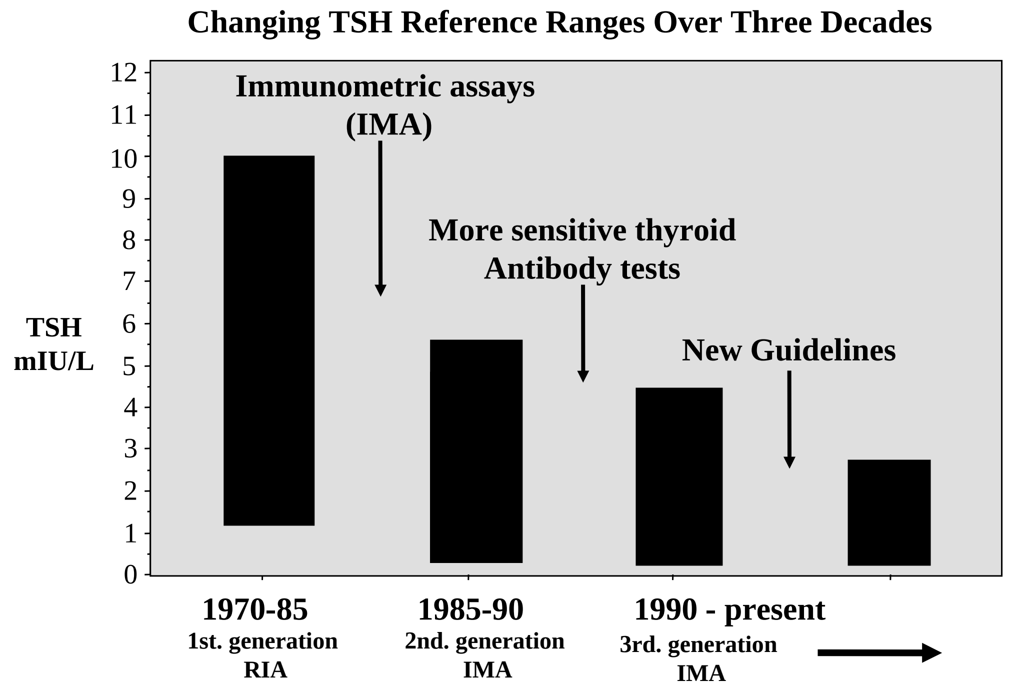

Changing TSH Reference Ranges Over Three Decades

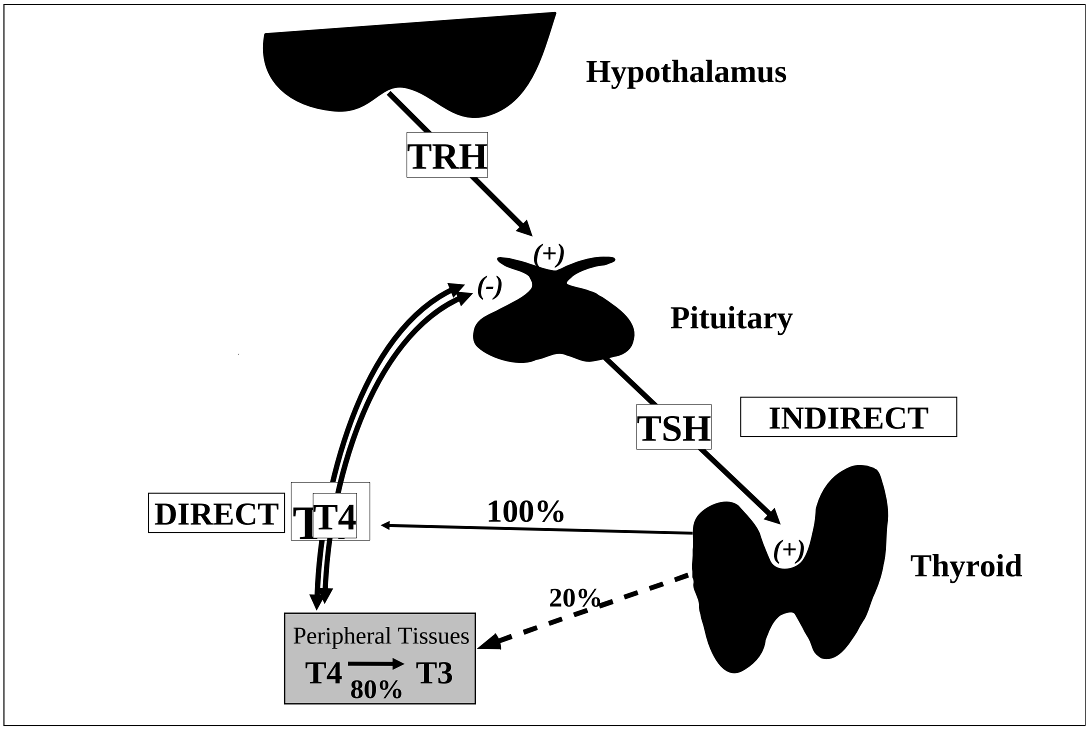
A review of TSH reference ranges across three decades shows that there has been a progressive contraction as a result of improvements in TSH sensitivity resulting from the development of immunuometric assays, coupled with improvements in thyroid antibody tests used to identify individuals with thyroid autoimmunity who have to be excluded from the reference cohort.

The contraction of the range has primarily affected the upper reference limit. New guidelines published in the last few years now recommend that the TSH upper limit be lowered still further down to 2.5 to 3.0 mIU/L.

OUTLINE
TSH Testing in Ambulatory Patients

- **Why TSH has become the primary thyroid test**
- **Limitations of using population reference ranges for the thyroid tests - TSH has a low index of individuality**
- **Rationale for a TSH lower reference limit of ~ 0.3 mIU/L**
- **Rationale for an empiric TSH upper reference limit of 2.5-3.0 mIU/L**
- **Clinical Rationale for adopting a TSH reference range 0.3-3.0 mIU/L**

This presentation will focus on TSH testing in ambulatory patients because most thyroid tests are made on outpatients.



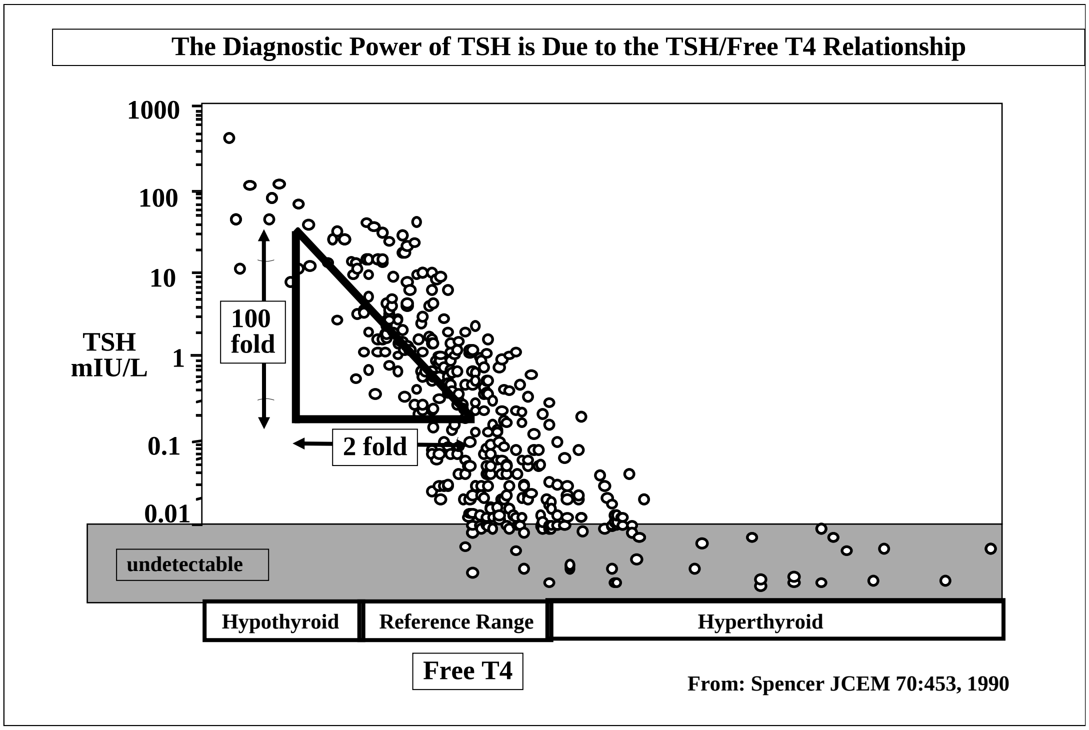
Thyroid activity is tightly controlled by the hypothalamic-pituitary axis. Specifically, hypothalamic TRH stimulates the pituitary to synthesize and secrete TSH - the primary trophic hormone that controls the biosynthesis and release of thyroid hormones, Thyroxine, T4 and Triiodothyronine, T3.

All T4 in the circulation is derived from the thyroid whereas only ~20% of T3 is a direct thyroid product,.The majority of circulating T3 comes from monodeiodination of T4 in peripheral tissues.

T4 is the thyroid hormone that is primarily responsible for the negative feedback on pituitary TSH secretion, completing the homeostatic loop.

It follows that there are two ways to assess thyroid function - the direct approach which is to measure the dominant thyroid hormone T4, usually as free hormone to overcome binding protein effects, or the indirect approach - TSH which will inversely reflect thyroid hormone status at the tissue level (I.e. the pituitary).

It has now become clear that the physiology of the hypothalamic-pituitary-thyroid axis dictates that TSH measurement is the most sensitive approach for detecting thyroid dysfunction.



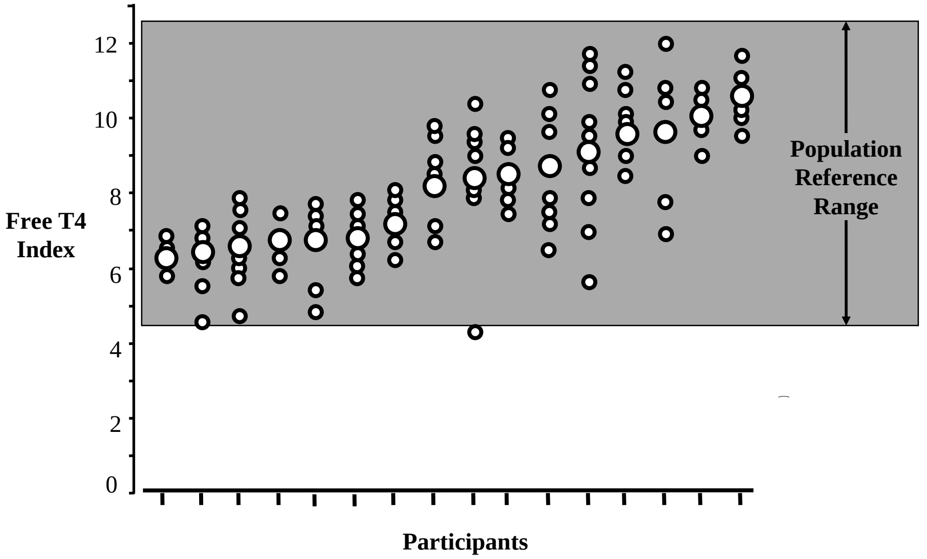
The Diagnostic Power of TSH is Due to the TSH/Free T4 Relationship

From: Spencer JCEM 70:453, 1990

The diagnostic power of TSH is due to the TSH/FT4 relationship which is the log/linear. This log/linear relationship dictates that free T4 abnormalities will be amplified with respect to change in TSH.

For example, a two-fold change in FT4 will produce a 100 fold change in TSH.

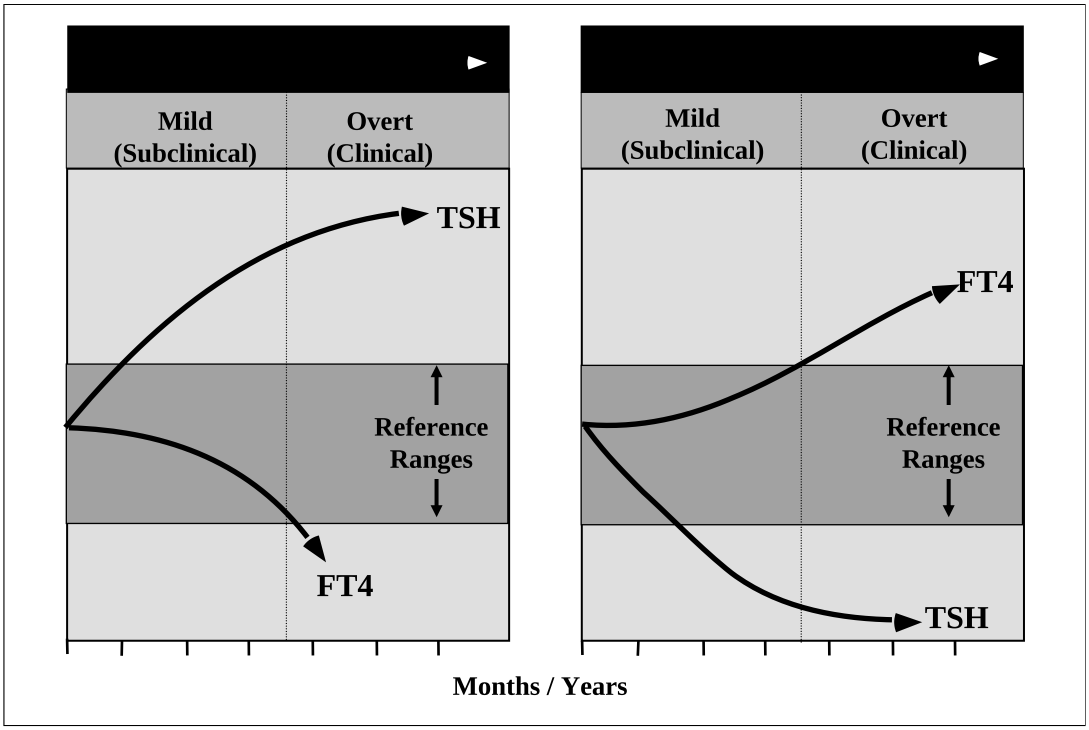
Individuals have a Genetically Controlled Free T4 Set-Point



Andersen et al JCEM 87: 1068, 2002

The reason is that TSH is so exquisitely sensitive to free T4 status is that individuals have a genetically determined free T4 setpoint, as illustrated by the study of Andersen in which free T4 was measured each month for a year period in 16 normal euthyroid individuals.

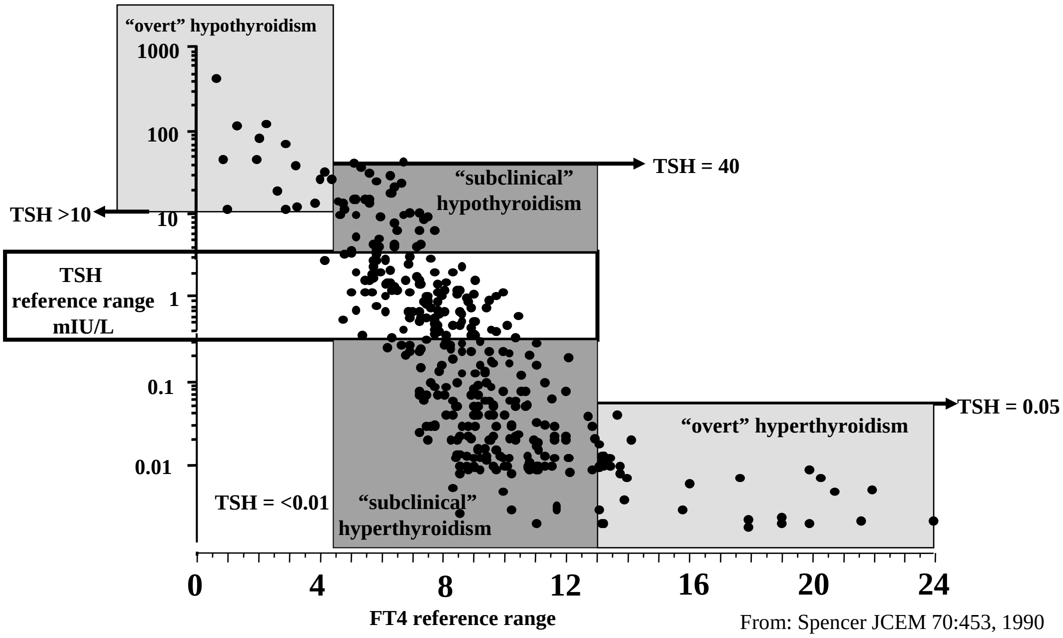
Although all the values fell within the population reference range, clearly the free T4 setpoint of some individuals was lower than for others.



It follows that in the course of developing hypo- or hyperthyroidism, TSH is the first abnormality to appear (as soon as the pituitary senses that free T4 has moved off it’s setpoint).

Mild (subclinical) disease is only detected as a TSH abnormality, whereas overt disease is considered present when both TSH and FT4 are outside their reference ranges.

Free T4 Status Does Not Always Indicate the Degree of Thyroid Dysfunction

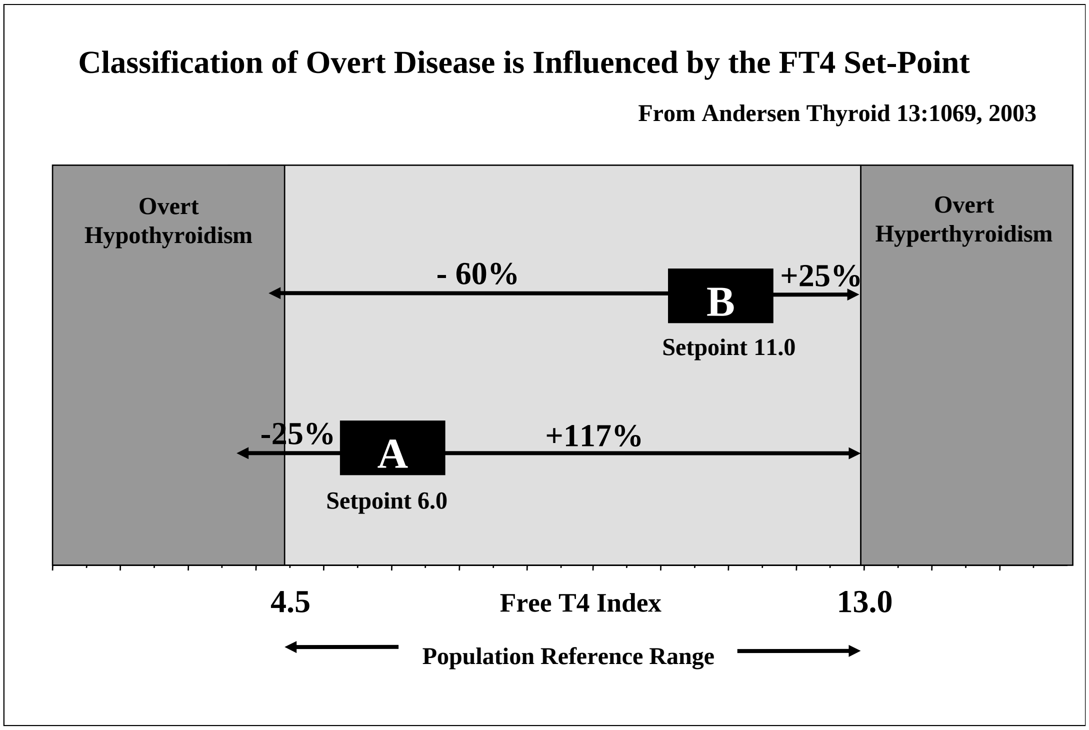


From: Spencer JCEM 70:453, 1990

It is important to recognize that free T4 status does not always indicate the degree of thyroid dysfunction.

The log/linear TSH/free T4 relationship dictates that an abnormal free T4 will not usually be seen unless TSH has risen above 10 mIU/L on the hypothyroid side, or has fallen below 0.05 mIU/L on the hyperthyroid side.

In contrast, patients can have TSH as high as 40 mIU/L or as low as undetectable (<0.01 mIU/L) without free T4 being abnormal. **This reflects differences in free T4 setpoints.**



Classification of Overt Disease is Influenced by the FT4 Set-Point

From Andersen Thyroid 13:1069, 2003

Overt Hypothyroidism

Overt Hyperthyroidism

- 60%

+25%

B

Setpoint 11.0

-25%

A

+117%

Setpoint 6.0

4.5

Free T4 Index

13.0

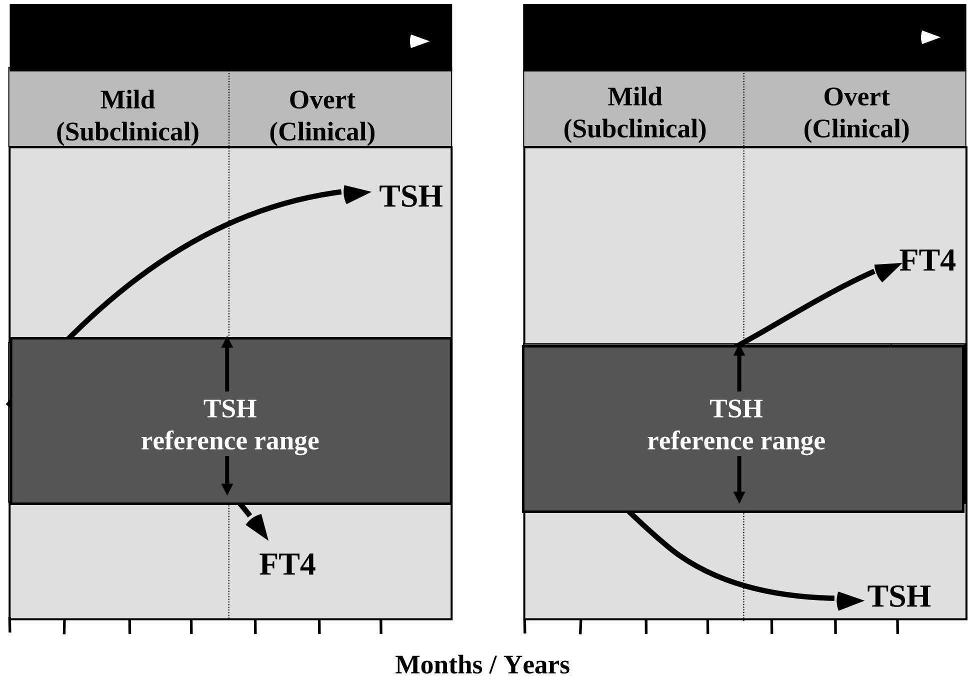
Population Reference Range

in fact, the classification of overt hypo- or hyperthyroidism is clearly influenced by the FT4 setpoint of the individual.

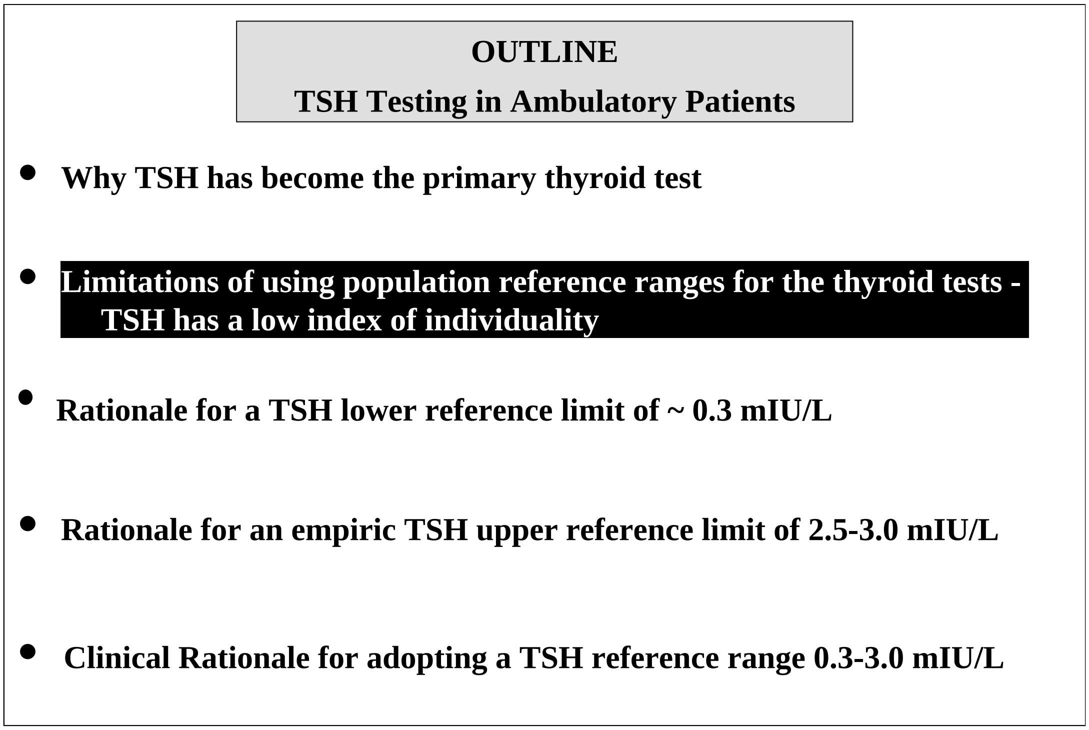
For example, the population reference range for free thyroxine (measured as a free T4 index) spans 3-fold from ~4.5 to ~13, yet the free T4 of individuals (for example Patient A with a FT4I setpoint of 6.0 and patient B with a set point of 11.0) only varies by about 1.5 (represented by the black box).

It follows that it would take only a 25% fall in the FT4I for patient A to be classified as being overtly hypothyroidism compared with a 60% fall in patient B.

Conversely, it would take more than a doubling of the FT4I of patient A before being classified as overtly hyperthyroidism compared to only a 25% rise in patient B.



Because TSH is the first abnormality to appear as disease develops, the accuracy of the setting of the TSH reference range becomes critical.



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TSH Testing in Ambulatory Patients

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- **Clinical Rationale for adopting a TSH reference range 0.3-3.0 mIU/L**

It is important to recognize the limitations of using population reference ranges for thyroid tests, all of which have a low index of individuality.

NACB Guideline 22

Thyroid 13:36, 2003

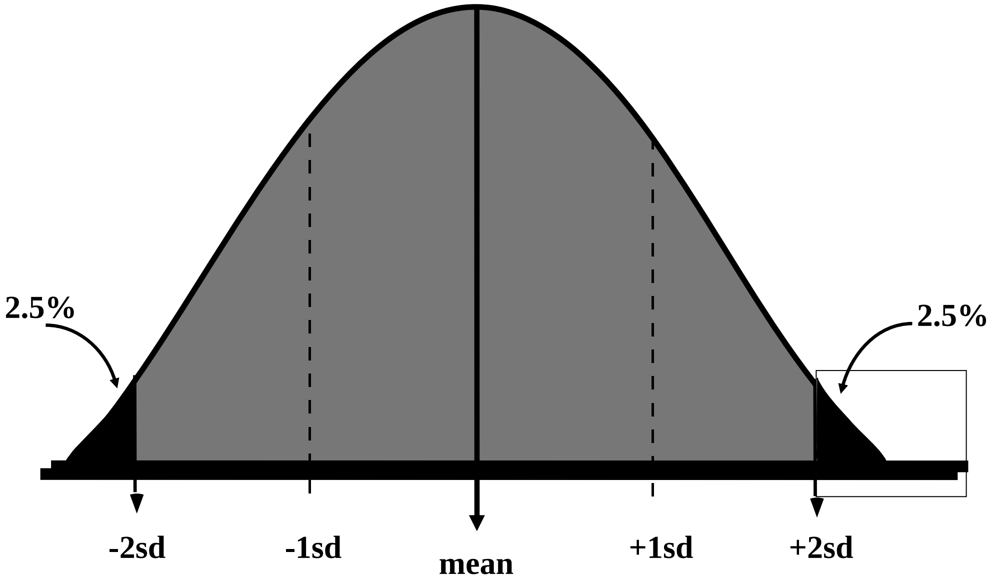
The TSH Reference Range

TSH reference intervals should be established from the 95 % confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers with:

- **No personal or family history of thyroid dysfunction**
- **No visible or palpable goiter**
- **No medications (except estrogen)**
- **No thyroid autoantibodies -TPOAb or TgAb (measured by sensitive immunoassay)**

Guidelines for establishing TSH reference ranges were recently published in the NACB guidelines.

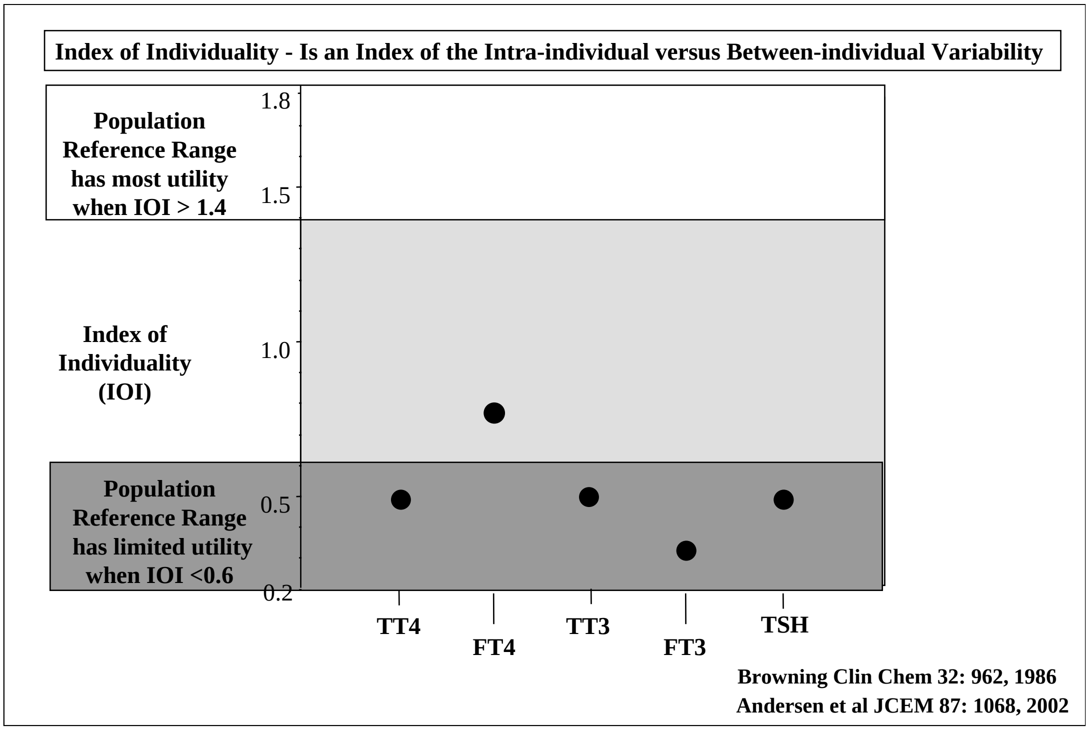
Reference
The TSH ~~Normal~~ Range



It is important to eliminate the concept of a “normal” range and replace it with the term “reference” range.

As with other biochemical tests, TSH reference ranges are typically established from the 95% confidence limits of a cohort of individuals thought to be free of thyroid dysfunction.

By definition, 2.5% of subjects will have a value that falls below the 2.5 percentile and 2.5% a value above the 97.5 percentile.



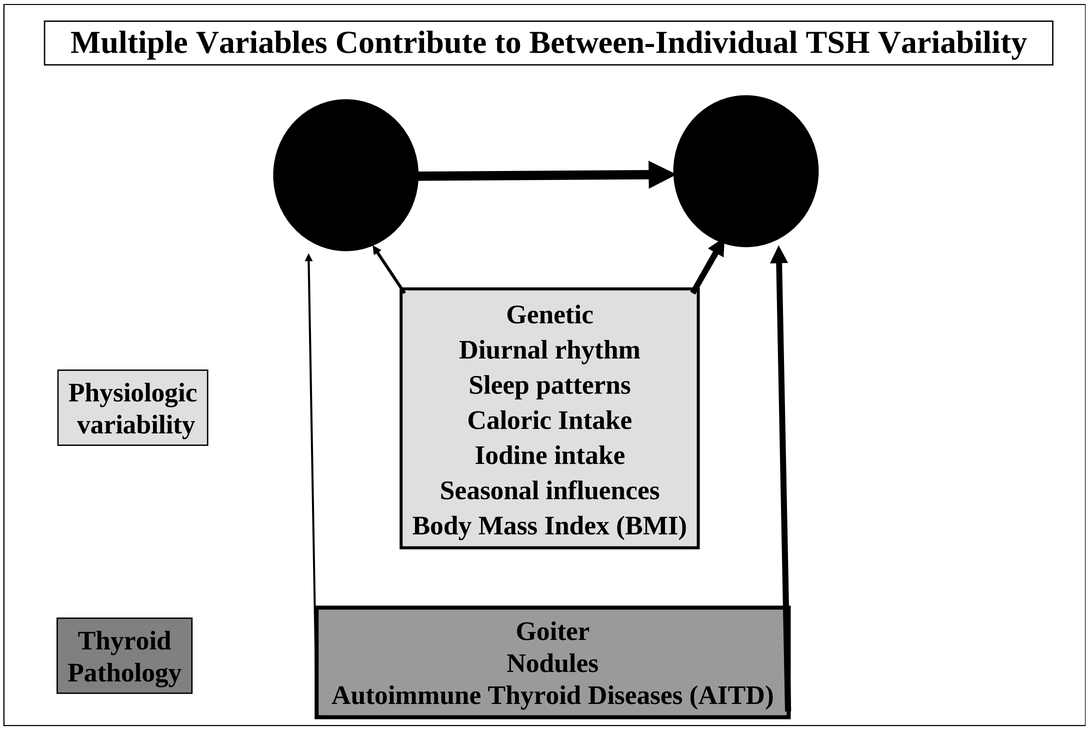
Index of Individuality - Is an Index of the Intra-individual versus Between-individual Variability

Browning Clin Chem 32: 962, 1986
Andersen et al JCEM 87: 1068, 2002

The index of individuality is a parameter that relates the between-person variability of a test to intra-individual variability.

It has been established that when the index of individuality (IOI) for a test is above1.4 the population reference range will have the most utility for diagnosing disease in an individual. In contrast, when the IOI is below 0.6 the population reference range has limited ability for detecting disease in the individual.

All of the thyroid tests, including TSH, have a low IOI, Indicating that the population reference ranges for thyroid tests will be crude parameters for detecting disease in individual patients.



Multiple Variables Contribute to Between-Individual TSH Variability

Physiologic variability

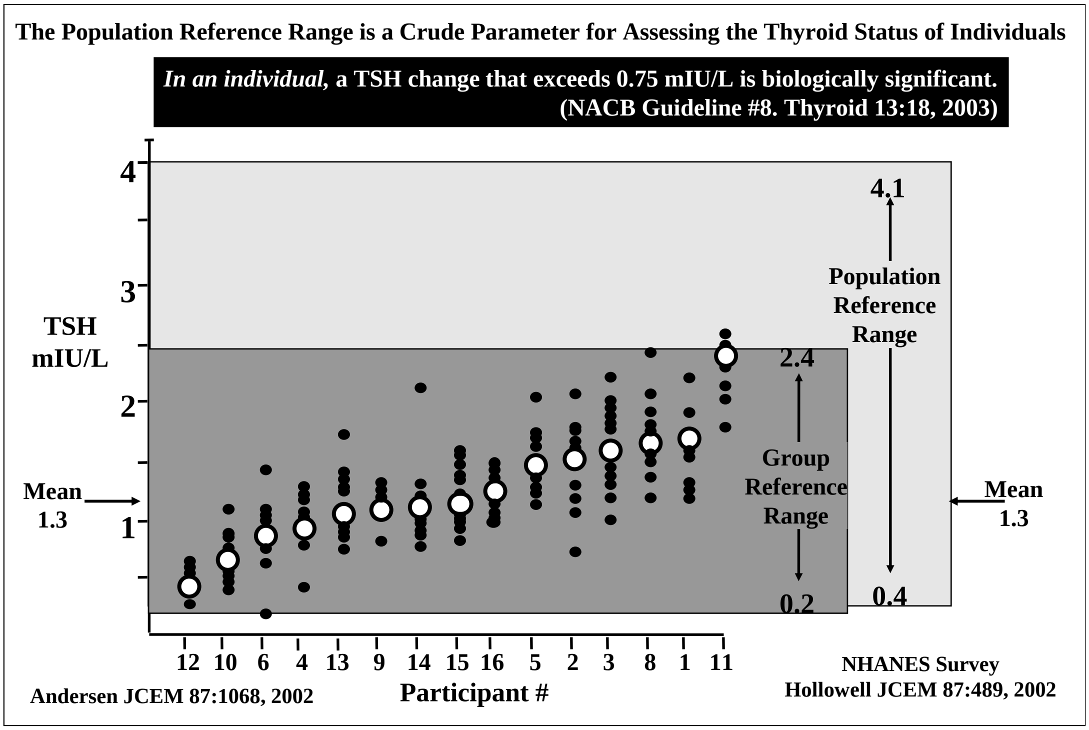
Genetic
Diurnal rhythm
Sleep patterns
Caloric Intake
Iodine intake
Seasonal influences
Body Mass Index (BMI)

Thyroid Pathology

Goiter
Nodules
Autoimmune Thyroid Diseases (AITD)

Individuals have different pathophysiologic factors that influence TSH. The combination of these variable in cohorts of individuals widen the TSH population reference range.

The most important variable is the presence of thyroid pathologies such as goiter, nodules and autoimmune thyroid diseases.



The Population Reference Range is a Crude Parameter for Assessing the Thyroid Status of Individuals

In an individual, **a TSH change that exceeds 0.75 mIU/L is biologically significant. (NACB Guideline #8. Thyroid 13:18, 2003)**

Andersen JCEM 87:1068, 2002

NHANES Survey
Hollowell JCEM 87:489, 2002

The typical NHANES US population reference range for TSH of 0.4 to 4.1 mIU/L (Hollowell JCEM 87:489, 2002) is much wider than the annual fluctuations in TSH typical of individuals (Anderson JCEM 87:1068, 2002).

In fact, in an individual a TSH change that exceeds 0.75 mIU/L is biologically significant.

Whereas the means and lower reference limits limits of the groups were essentially the same, the difference was in the setting of the upper reference limit.

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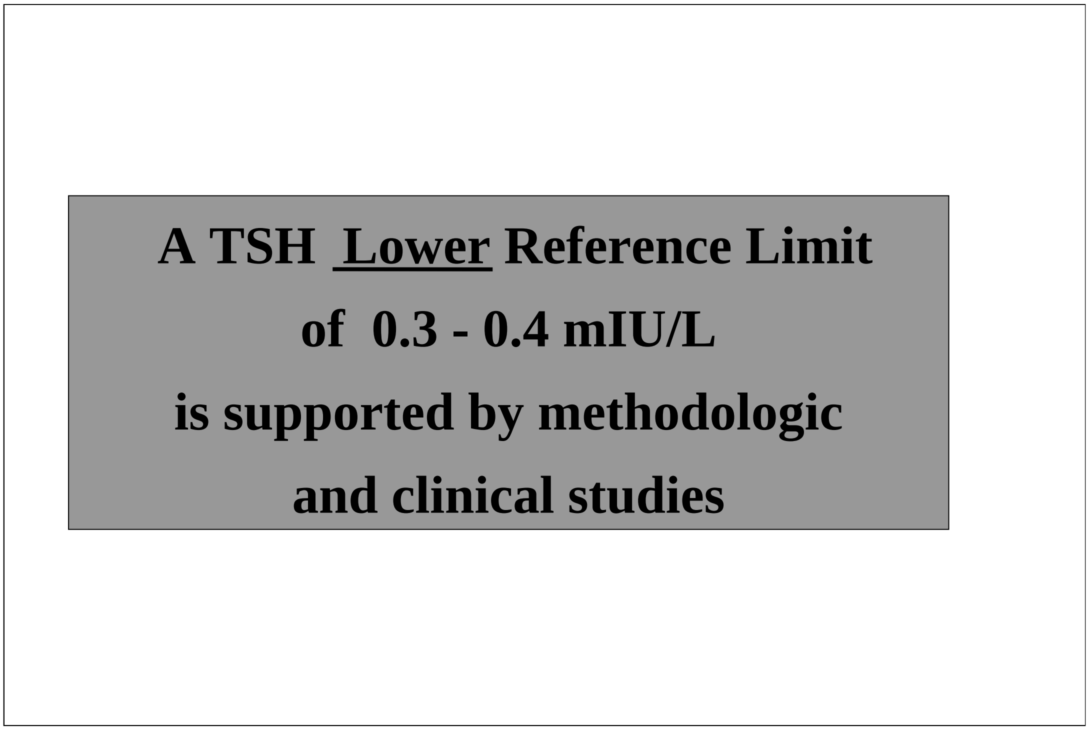
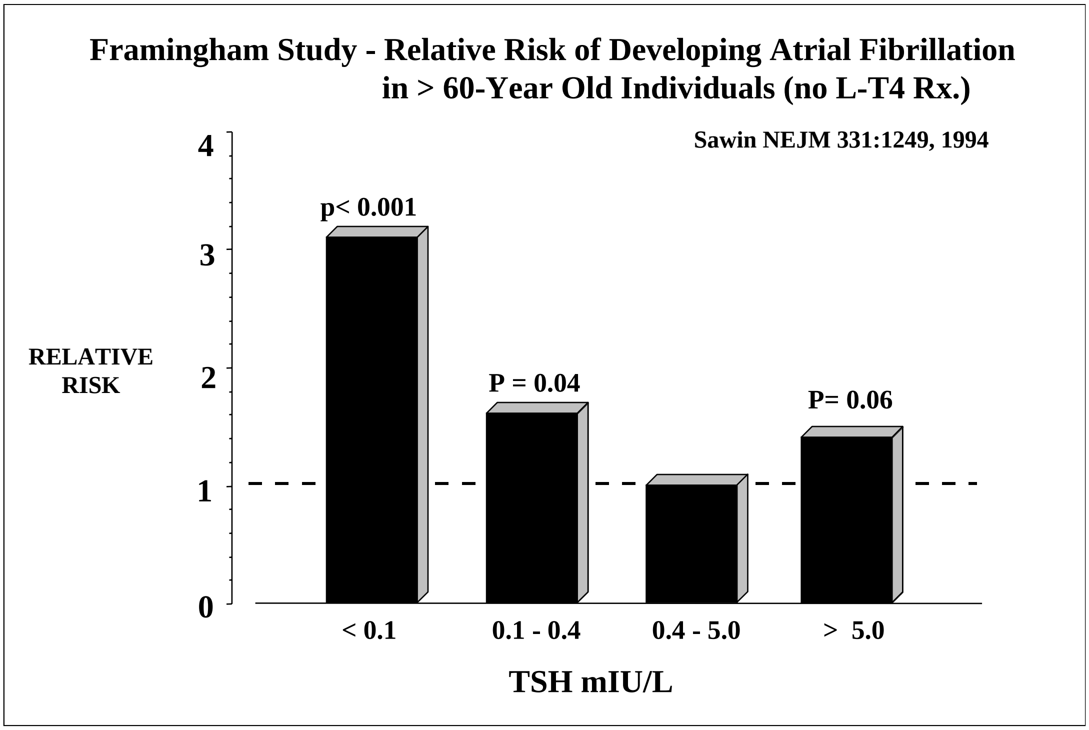
There is good rationale for setting the TSH lower reference limit around 0.3 mIU/L.



A TSH Lower Reference Limit of 0.3 - 0.4 mIU/L is supported by methodologic and clinical studies

A TSH lower reference limit of 0.3-0.4 mIU/L is supported by both methodolologic and clinical studies.



Framingham Study - Relative Risk of Developing Atrial Fibrillation in > 60-Year Old Individuals (no L-T4 Rx.)

Sawin NEJM 331:1249, 1994

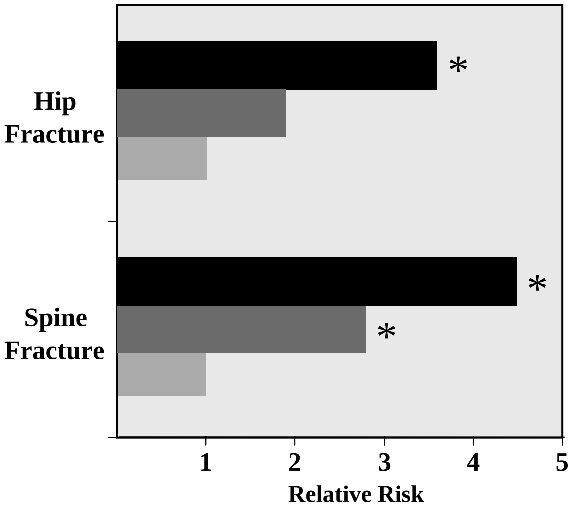
For example, the Framingham study reported that in individuals over 60 years of age who were not taking levothyoxine with TSH below 0.1 mIU/L had a 3-fold increased the risk of developing atrial fibrillation (AF).

Even a minor suppression in TSH into the 0.1-0.4 mIU/L range significantly increased the relative risk of AF.

Subclinical Hyperthyroidism -
The Study of Osteoporotic Fractures

Bauer DC et al AIM 134:561-568, 2001

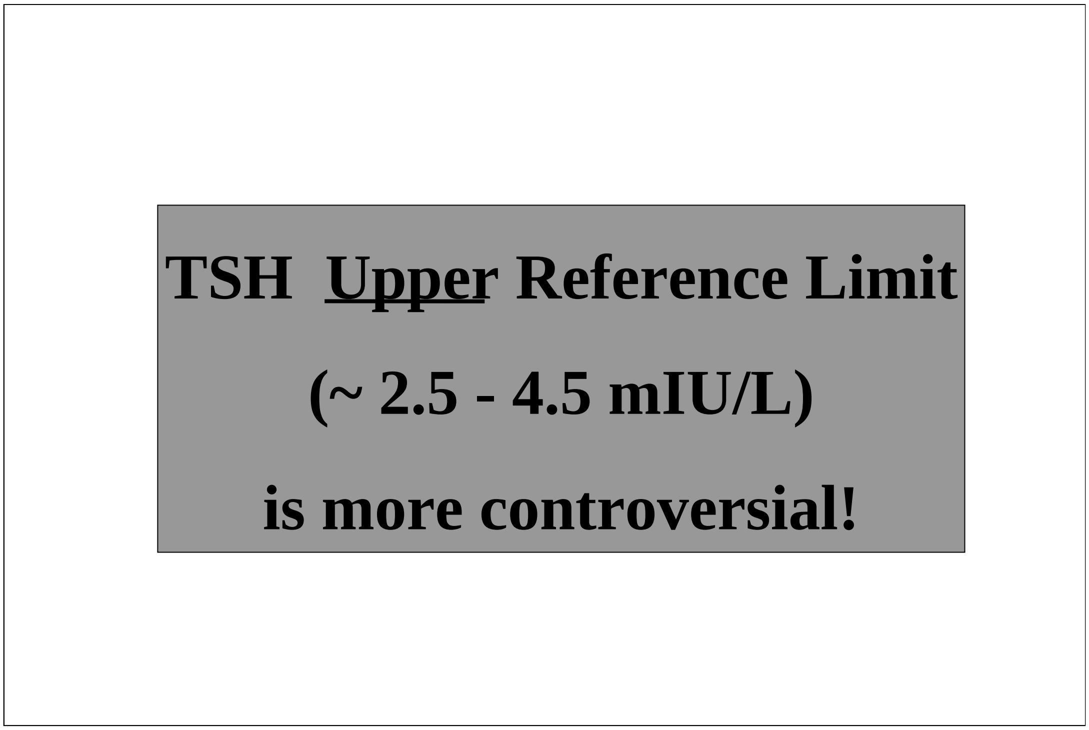
- **Prospective Cohort Study**
- **686 from Cohort of 9704 women**
- **Age >65 yrs**
- **Data Adjusted by Multifactorial Analysis**
  1. **Previous Hyperthyroidism**
  2. **Age**
  3. **Self-Rated Health**
  4. **Estrogen Use**
  5. **Thyroid Hormone Use**



■ TSH <0.1
▨ TSH 0.1-0.5
□ TSH 0.5-5.5

The Bauer study suggests that there is an increased risk of osteoporotic fractures in older women with low TSH.

This increased risk of osteoporotic fractures was even seen in individuals with only marginally suppressed TSH (0.1 - 0.5 mIU/L), especially in the spine.



TSH Upper Reference Limit

(~ 2.5 - 4.5 mIU/L)

is more controversial!

In contrast to the TSH lower reference limit, the upper reference limit is more controversial and is variously cited as being between 2.5 and 4.5 mIU/L.

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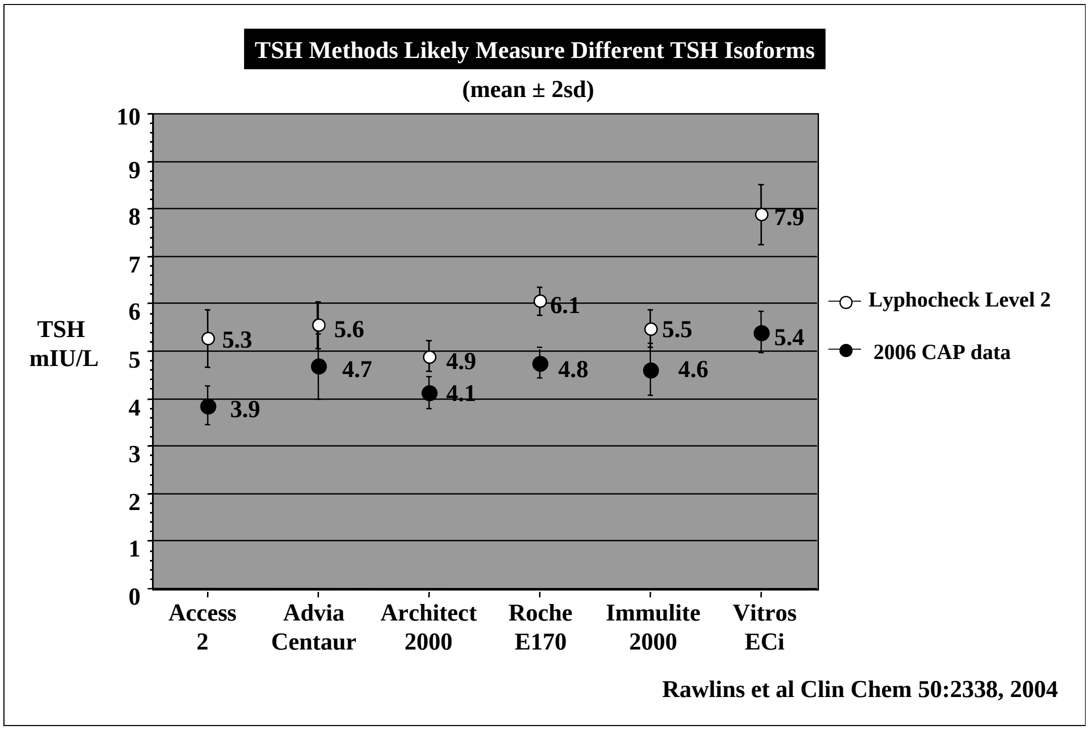
There is rationale for setting an empiric TSH upper limit between 2.5 and 3.0 mIU/L.



TSH Methods Likely Measure Different TSH Isoforms

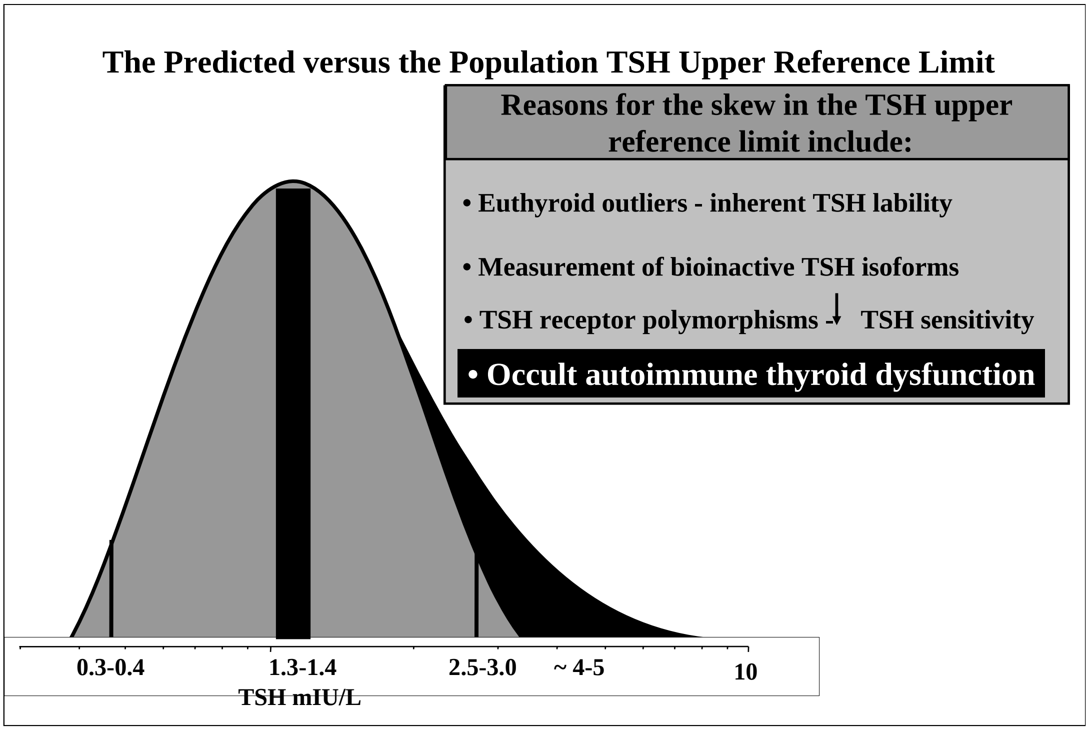
(mean ± 2sd)

Rawlins et al Clin Chem 50:2338, 2004

TSH in the circulation is heterogeneous both with respect to glycosylation and biologic activity.

Current TSH immunometric assays that employ monoclonal antibodies with limited specificity likely measure different TSH isoforms because there is more variability among assays that are all standardized against the same IRP than would be explained by methodologic variabliity alone.

These specificity differences are an added variable that makes the setting of a universal upper TSH reference limit impossible.



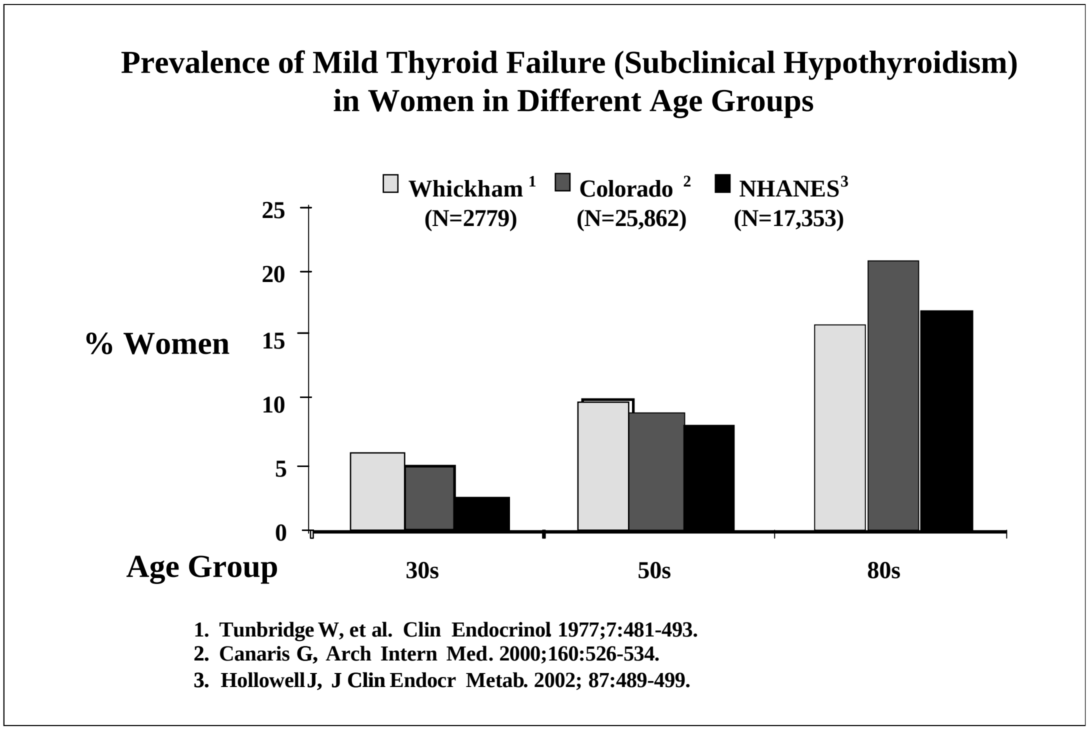
The Predicted versus the Population TSH Upper Reference Limit

Reasons for the skew in the TSH upper reference limit include:

- **Euthyroid outliers - inherent TSH lability**
- **Measurement of bioinactive TSH isoforms**
- **TSH receptor polymorphisms - ↓ TSH sensitivity**
- **Occult autoimmune thyroid dysfunction**

Given that there is good rationale for a lower TSH reference limit limit in the 0.3 to 0.4 mIU/L range and a mean around 1.3 to 1.4 mIU/L, a Gaussian distribution would project a TSH upper limit between 2.5 and 3.0 mIU/L and not 4 to 5 mIU/L, as reported by population studies.

There are a number of causes for the skew in the TSH upper reference limit, however the most significant is the inclusion of individuals with occult autoimmune thyroid dysfunction.



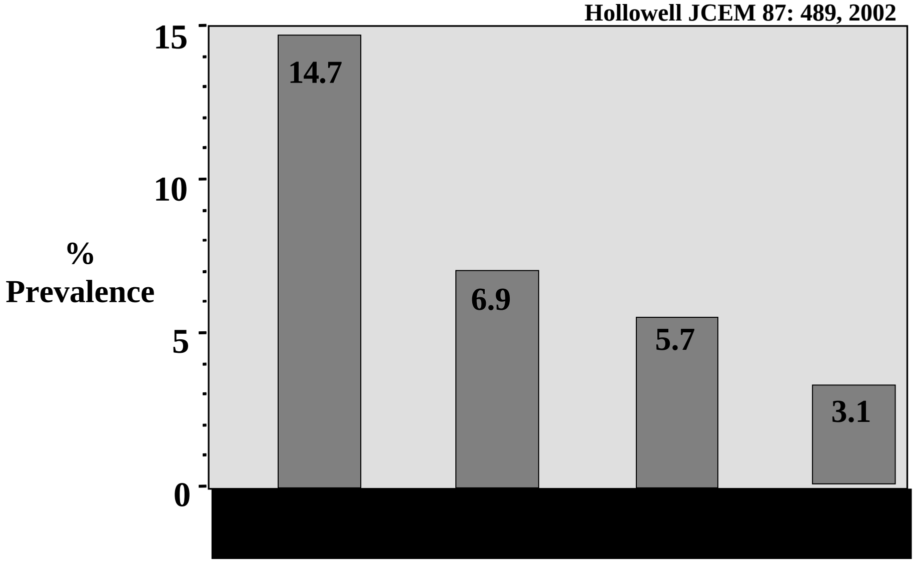
Prevalence of Mild Thyroid Failure (Subclinical Hypothyroidism) in Women in Different Age Groups

1. Tunbridge W, et al. Clin Endocrinol 1977;7:481-493.
2. Canaris G, Arch Intern Med. 2000;160:526-534.
3. Hollowell J, J Clin Endocr Metab. 2002; 87:489-499.

It is not surprising that the cohorts used to establish TSH reference ranges are contaminated with individuals with autoimmune thyroid dysfunction, because autoimmune thyroid disease, especially Hashimotos' thyroiditis leading to hypothyroidism, is very common. The prevalence of mild thyroid failure (subclinical hypothyroidism) is high in women and increases with age, as shown by three large population surveys.

NHANES - Prevalence of Thyroid Antibodies (n= 17,353)

Hollowell JCEM 87: 489, 2002



Odds Ratio for Overt Hypothyroidism	23.5	6.9	1.1
Odds Ratio for Subclinical Hypothyroidism	11.7	4.0	1.5

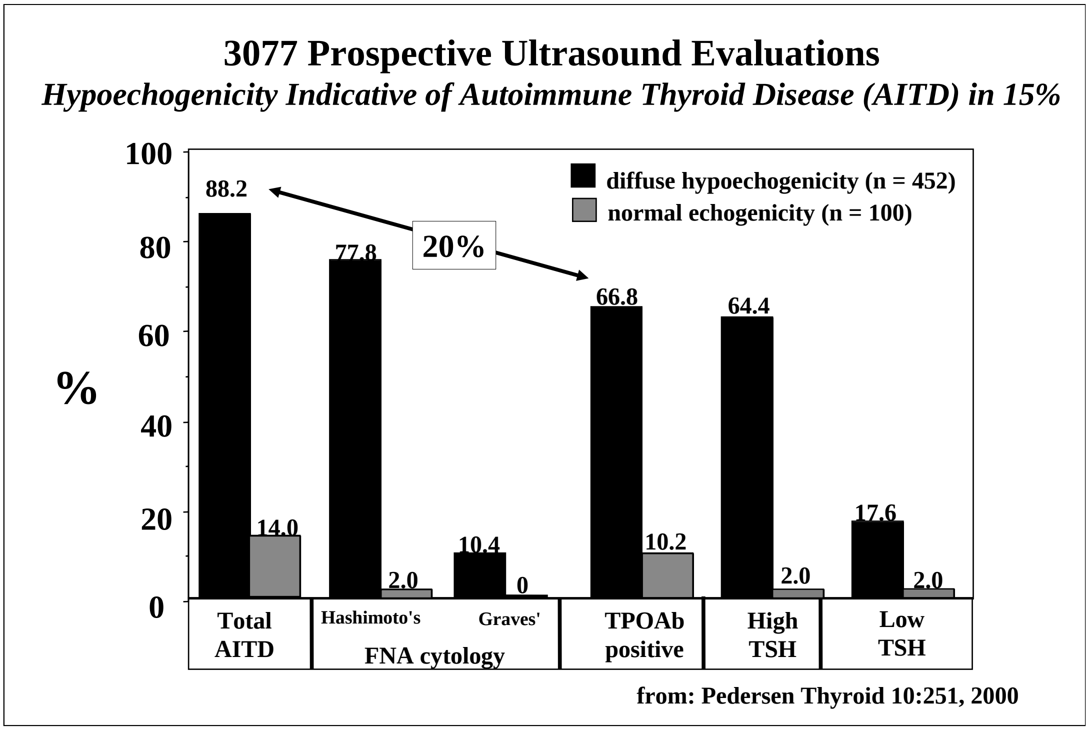
As reported by the NHANES survey, thyroid autoantibodies, a marker of thyroid autoimmunity are especially prevalent in the US population. Thyroid peroxidase antibodies (TPOAb), the dominant type of antibody were often associated with Thyroglobulin antibodies (TgAb).

Importantly, the odds ratios for both overt and subclinical hypothyroidism were strongly associated with the presence of TPOAb especially when associated with TgAb, but not TgAb alone. It follows that when making a diagnosis of thyroid autoimmunity TPOAb is the only antibody test usually needed.

The presence of TPO antibodies (TPOAb) is the primary exclusion criterion for autoimmune thyroid disease when establishing TSH reference ranges

However, TPOAb is not always detected in patients with AITD!

The presence of TPOAb is the primary criterion for excluding subjects with autoimmune thyroid disease (AITD) from cohorts used to establish TSH reference limits, However,TPOAb is not always detected in patients with AITD.



3077 Prospective Ultrasound Evaluations

Hypoechogenicity Indicative of Autoimmune Thyroid Disease (AITD) in 15%

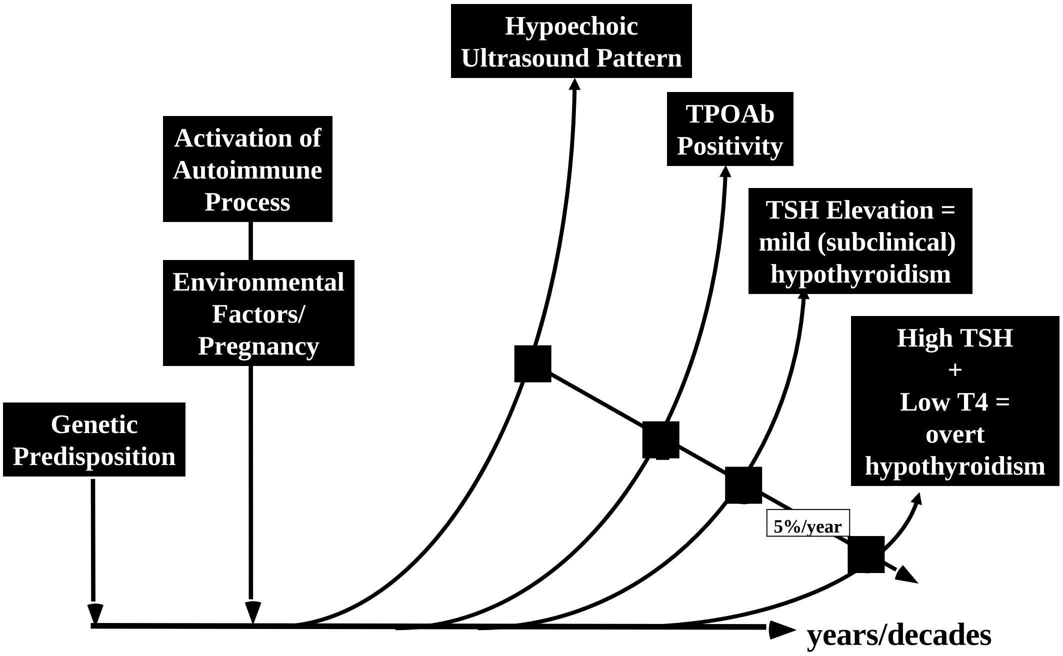
from: Pedersen Thyroid 10:251, 2000

Ultrasound can detect thyroid autoimmunity because a hypoechoic ultrasound pattern indicates lymphocytic infiltration. In a study of over 3000 prospective ultrasounds ordered for a variety of reasons, nearly 15% of subjects displayed evidence of hypoechogenicity.

When these subjects were compared with controls having normal echogenicity, autoimmune thyroid dysfunction was confirmed by cytology in over 88% of cases compared with only 14% in controls.

Important to note was that >20% of the individuals with evidence of thyroid autoimmunity had no TPOAb detected.

Developing Autoimmune Thyroid Dysfunction



Hypoechoic Ultrasound Pattern

TPOAb Positivity

Activation of Autoimmune Process

TSH Elevation = mild (subclinical) hypothyroidism

Environmental Factors/ Pregnancy

High TSH + Low T4 = overt hypothyroidism

Genetic Predisposition

5%/year

years/decades

In the course of progressive Hashimotos’ thyroiditis a hypoechoic ultrasound pattern suggesting lymphocytic infiltration, often occurs before the detection of TPOAb .

Thereafter, with progression of disease, mild (subclinical) hypothyroidism (isolated high TSH) develops and subclinical hypothyroidism is known to progress to overt hypothyroidism (high TSH/low FT4) at a rate of ~5%/year.

This progression is part of the same pathologic autoimmune process that eventually leads to overt hypothyroidism at different rates in different individuals.

Occult Thyroid Dysfunction Skews the TSH Upper Limit

Recommendations: Adopt an *Empiric* TSH Upper Limit

- **National Academy of Clinical Biochemistry (NACB) Guidelines:**

Ambulatory patients with a serum TSH above 2.5 mIU/L,
when confirmed by a repeat TSH measurement made
after 3 weeks, may be in the early stages of thyroid failure,
especially if TPOAb is detected.

Thyroid 13:42, 2003 & www nacb.org

- **Association of Clinical Endocrinologists (AACE) Guidelines:**

Proposes the adoption of a TSH reference range of 0.3 - 3.0 mIU/L

Endocrine Practice 8:457, 2002

The recognition that occult thyroid dysfunction skews population TSH reference limits has led to recommendations from the NACB and the AACE that an empiric TSH upper reference limit between 2.5 and 3.0 mIU/L be adopted.

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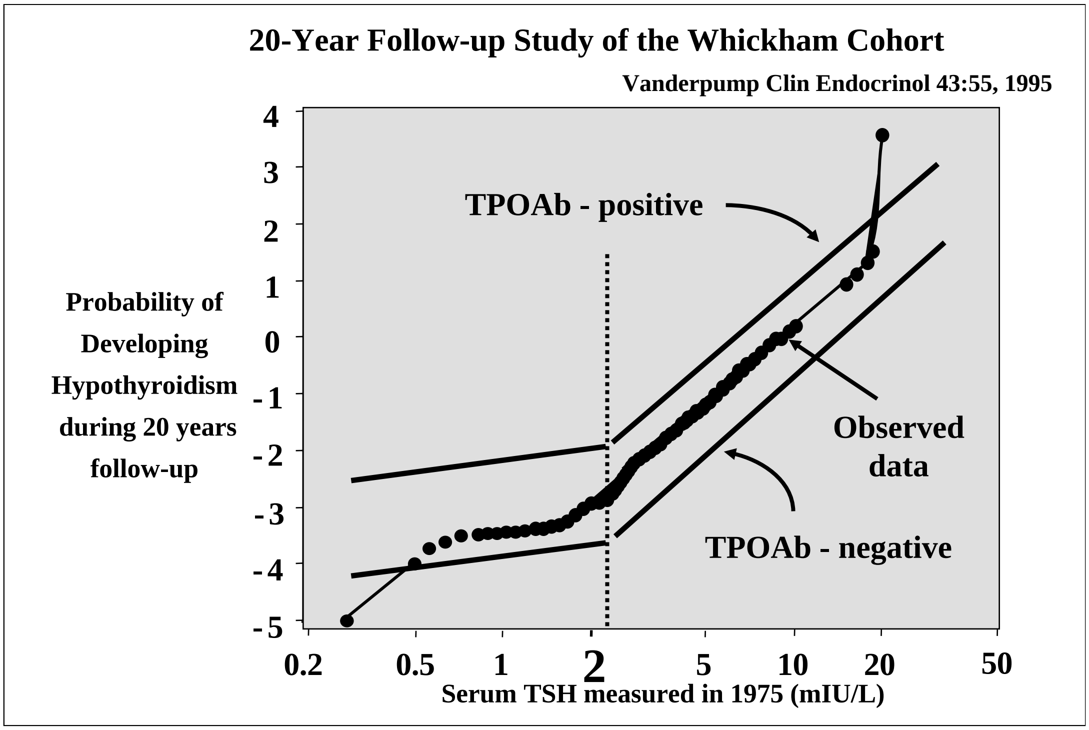
There is strong clinical rationale for adopting a TSH reference range of 0.3 to 3.0 mIU/L.



20-Year Follow-up Study of the Whickham Cohort

Vanderpump Clin Endocrinol 43:55, 1995

We know from the Whickham 20-year follow-up survey that a TSH above ~2 mIU/L is a risk factor for the future development of hypothyroidism, especially when TPOAb is detected.

However, even in the absence of thyroid antibodies an increased risk was evident.

A TSH Upper Reference Limit of 2.5 mIU/L is now Considered Optimal for Managing Pregnant Patients.

Growing recognition that even

mild (subclinical) Thyroxine deficiency

in early pregnancy is

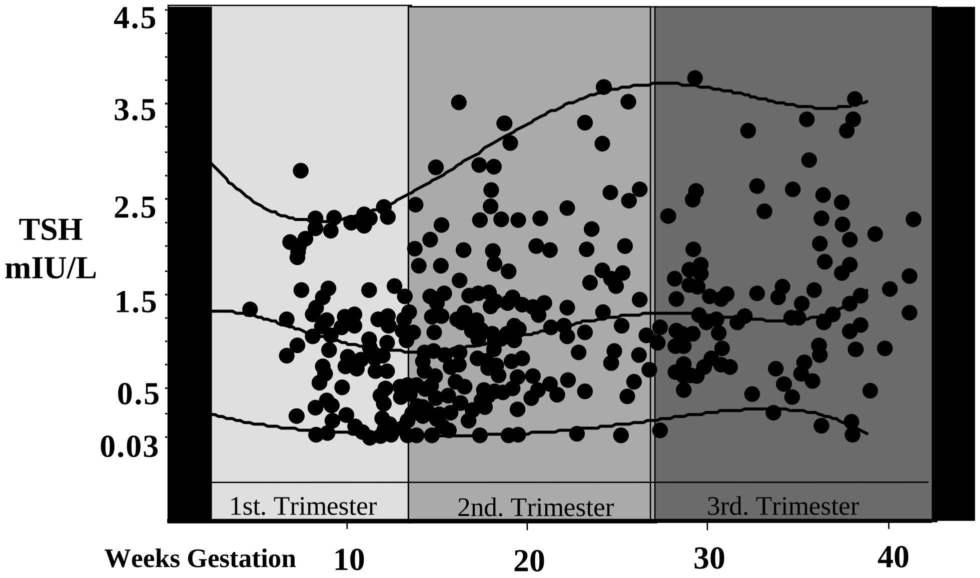
detrimental to mother and fetus

New guidelines state that a TSH below 2.5 mIU/L is optimal for pregnancy.

Mandel et al Thyroid 15:44, 2005
Casey et al Obstet Gynecol 105:239,2005

The empiric lowering of the TSH upper reference limit to 2.5 mIU/L is further justified because of the growing **recognition that even mild (subclinical) Thyroxine deficiency in early pregnancy is detrimental to mother and fetus.** New **guidelines now**

Changes in TSH During Pregnancy

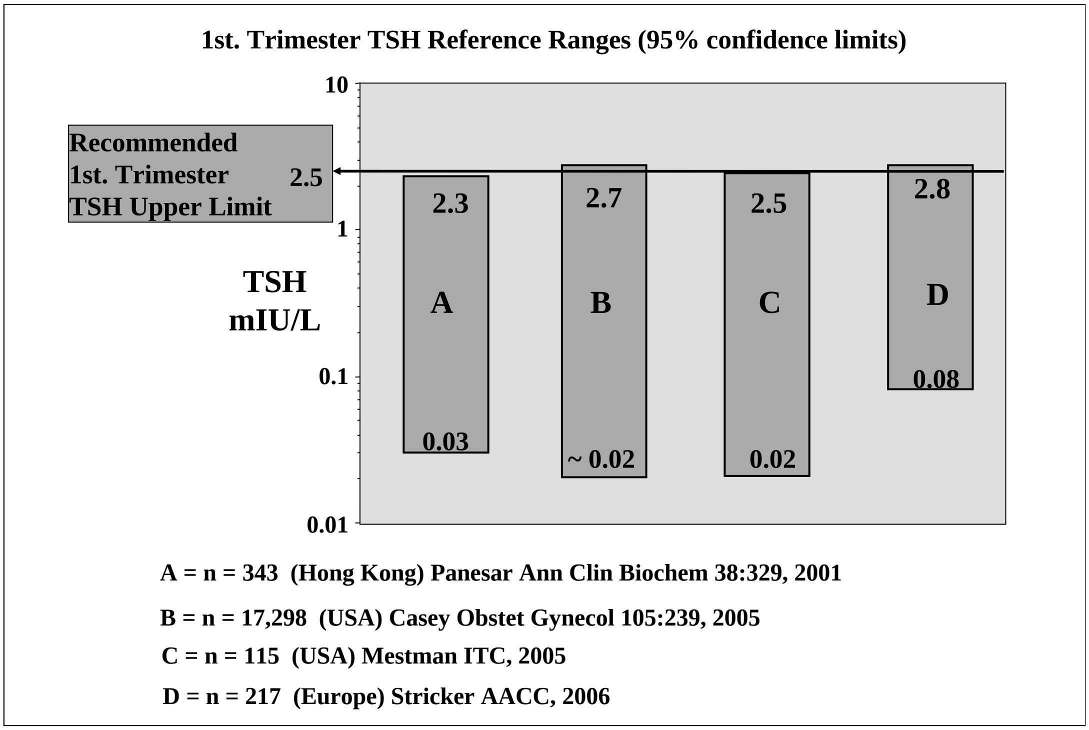


Panesar Ann Clin Biochem 38: 329, 2001

Mandel et al Thyroid 15:44, 2005

Longitudinal studies show that TSH is typically suppressed to some degree in the first trimester as a result of hCG stimulation of the thyroid that slightly raises free T4.

This is likely to be a physiological adaptation to ensure the delivery of sufficient maternal thyroxine to the developing fetus during the time before the fetal thyroid becomes active (~13 weeks).



1st. Trimester TSH Reference Ranges (95% confidence limits)

A = n = 343 (Hong Kong) Panesar Ann Clin Biochem 38:329, 2001

B = n = 17,298 (USA) Casey Obstet Gynecol 105:239, 2005

C = n = 115 (USA) Mestman ITC, 2005

D = n = 217 (Europe) Stricker AACC, 2006

A number of studies now support the use of a TSH upper reference limit of 2.5mIU/L in the first trimester.

Question

In the non-pregnant patient,

do mild TSH abnormalities

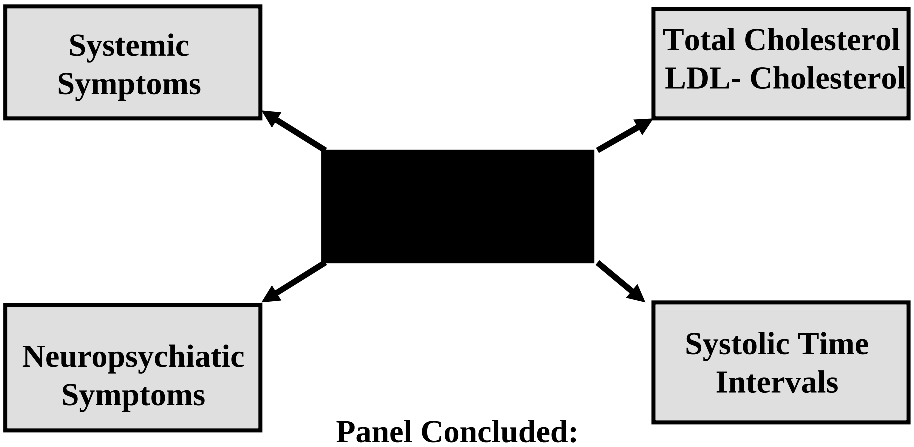
(TSH > 3.0 mIU/L)

have any clinical significance?

An important question is whether in non-pregnant patients a TSH above 2.5 mIU/L has any clinical significance?

2002 Consensus Conference Reviewed Literature between 1995 and 2002

Surks et al JAMA 291:228, 2004



Panel Concluded:

“Few symptoms and little benefit in treating Subclinical Hypothyroidism when TSH is < 10 mIU/L”

This question was addressed by a consensus conference 2002 that reviewed studies published between 1995 and 2002 focusing on whether subclinical hypothyroidism was associated with systemic or neurophychiatric symptoms, changes in cholesterol status or alterations in systolic time intervals.

The panel concluded that there were few symptoms and little benefit treating subclinical hypothyroidism when TSH was below 10 mIU/L

2002 Subclinical Hypothyroidism (SCHO) Consensus Conference

Problems

- **Many studies were based on small numbers of subjects and most were not double-blinded, placebo-controlled trials.**
- **SCHO study groups often included individuals with different degrees of severity (i.e. subjects with TSH below & above 10 mIU/L were grouped).**
- **In some studies claiming a lack of a treatment response suboptimal L-T4 treatment was employed that failed to lower TSH below 3.0 mIU/L.**
- **Typically, insensitive parameters (like symptoms & Total Cholesterol) were used to judge the effects of SCHO.**

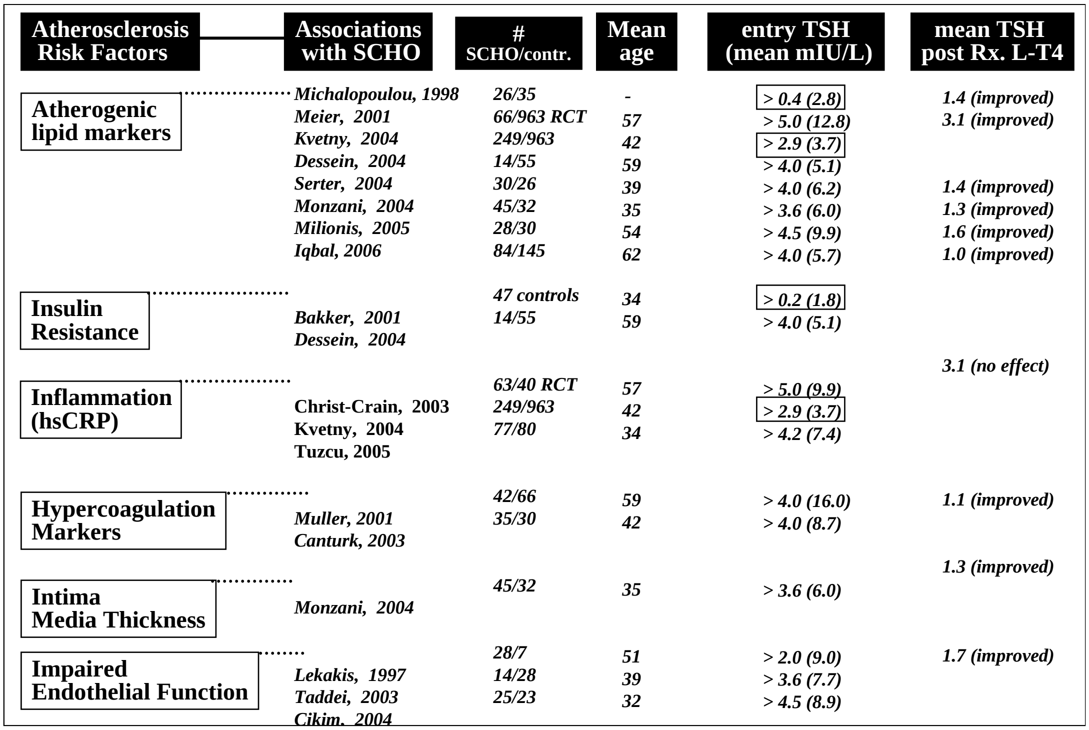
The literature that supported this conclusion had a number of problems:

Most studies have been based on small numbers of subjects and most have not been double-blinded, placebo-controlled trials.

The subclinical hypothyroid study groups often included individuals with different degrees of severity, I.e. subjects with TSH below and above 10 mIU/L have been grouped.

Some studies claiming a lack of a treatment response used suboptimal L-T4 doses that have failed to lower TSH below 3.0 mIU/L.

Typically insensitive tissue parameters like symptoms and total cholesterol were used to judge whether subclinical hypothyroidism was associated with clinical effects.



Atherosclerosis Risk Factors	Associations with SCHO	# SCHO/contr.	Mean age	entry TSH (mean mIU/L)	mean TSH post Rx. L-T4
Atherogenic lipid markers	*Michalopoulou, 1998*	*26/35*	-	$\boxed{> 0.4\ (2.8)}$	*1.4 (improved)*
	Meier, 2001	*66/963 RCT*	*57*	*> 5.0 (12.8)*	*3.1 (improved)*
	Kvetny, 2004	*249/963*	*42*	$\boxed{> 2.9\ (3.7)}$	
	Dessein, 2004	*14/55*	*59*	*> 4.0 (5.1)*	
	Serter, 2004	*30/26*	*39*	*> 4.0 (6.2)*	*1.4 (improved)*
	Monzani, 2004	*45/32*	*35*	*> 3.6 (6.0)*	*1.3 (improved)*
	Milionis, 2005	*28/30*	*54*	*> 4.5 (9.9)*	*1.6 (improved)*
	Iqbal, 2006	*84/145*	*62*	*> 4.0 (5.7)*	*1.0 (improved)*
Insulin Resistance		*47 controls*	*34*	$\boxed{> 0.2\ (1.8)}$	
	Bakker, 2001	*14/55*	*59*	*> 4.0 (5.1)*	
	Dessein, 2004				
					3.1 (no effect)
Inflammation (hsCRP)		*63/40 RCT*	*57*	*> 5.0 (9.9)*	
	Christ-Crain, 2003	*249/963*	*42*	$\boxed{> 2.9\ (3.7)}$	
	Kvetny, 2004	*77/80*	*34*	*> 4.2 (7.4)*	
	Tuzcu, 2005				
Hypercoagulation Markers		*42/66*	*59*	*> 4.0 (16.0)*	*1.1 (improved)*
	Muller, 2001	*35/30*	*42*	*> 4.0 (8.7)*	
	Canturk, 2003				
					1.3 (improved)
Intima Media Thickness		*45/32*	*35*	*> 3.6 (6.0)*	
	Monzani, 2004				
Impaired Endothelial Function		*28/7*	*51*	*> 2.0 (9.0)*	*1.7 (improved)*
	Lekakis, 1997	*14/28*	*39*	*> 3.6 (7.7)*	
	Taddei, 2003	*25/23*	*32*	*> 4.5 (8.9)*	
	Cikim, 2004				

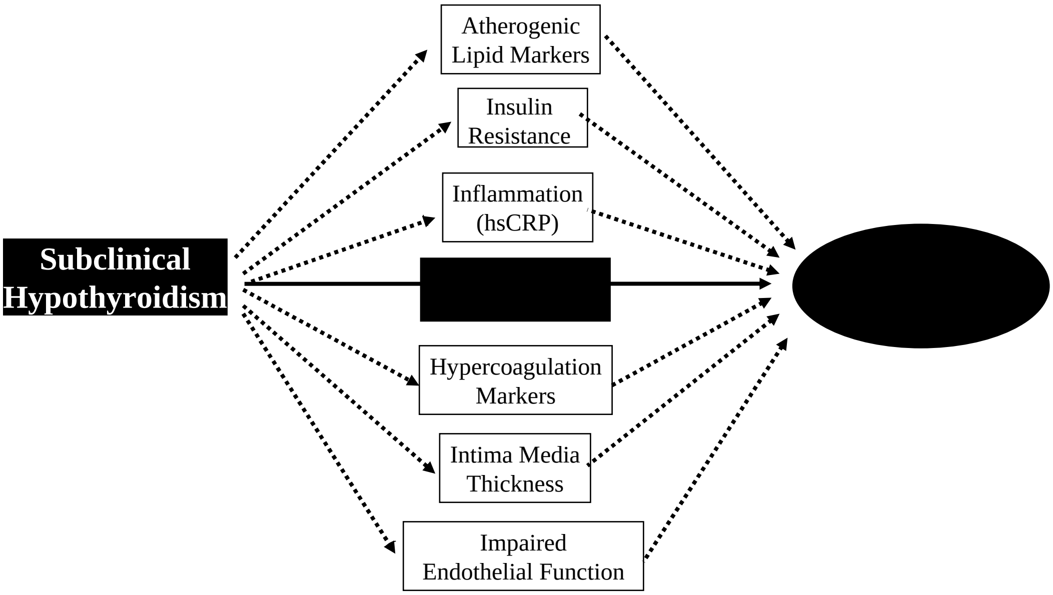
Since 2002 a growing number of studies have been published suggesting that there is indeed an association between risk factors for atheroscleroisis and subclinical hypothyroidism.

These studies have begun to look at more sensitive markers of atherosclerosis risk.

Most studies are still only small and few are placebo controlled and double blinded and some that assessed the response to L-T4 treatment still failed to achieve a target TSH below 2.0 mIU/L. However, most of those with a treatment arm did show improvements of the study parameter in question with L-T4 treatment.

The most striking difference between the earlier and more recent studies has been the focus on very mild subclinical hypothyroidism - subjects having a TSH below 10 mIU/L.

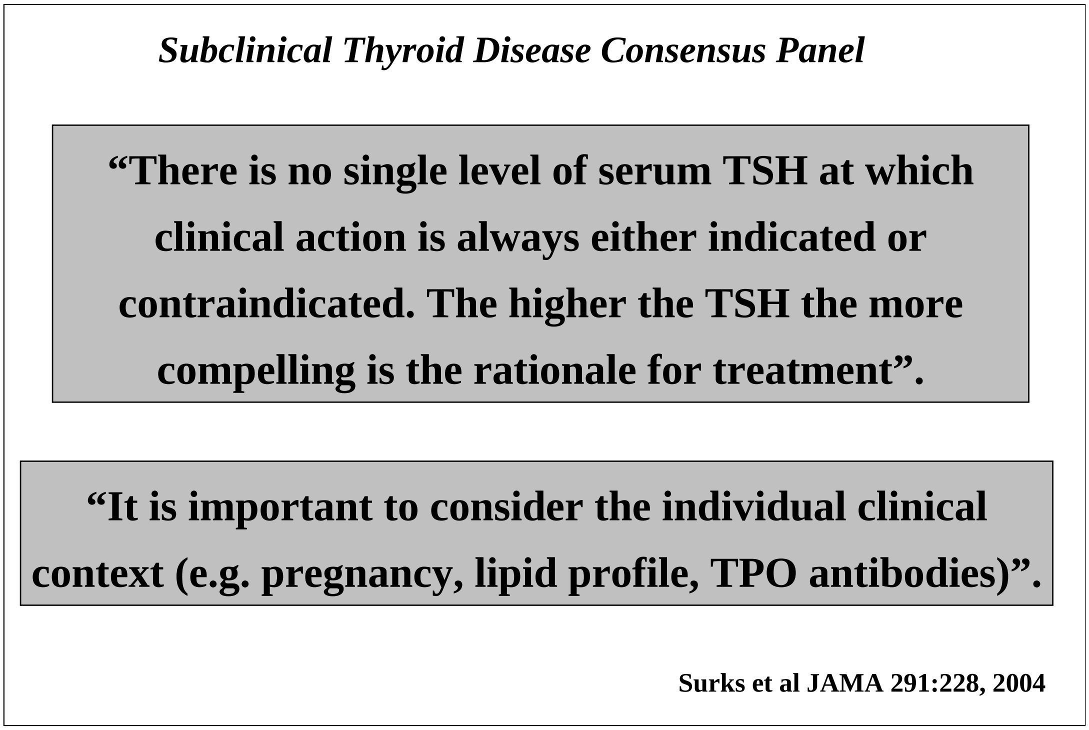
The bracketed studies have even reported significant relationships between the study parameter and TSH values below 4.0 mIU/L.



There is wide between-subject differences in overall cardiovascular risk.
Subject selection (SCHO vs control) likely accounts for the variability among studies.

It follows that there is growing evidence suggesting that subclinical hypothyroidism is a risk factor for cardiovascular disease through a number of mechanisms associated with the development of atherosclerosis.

However, it is important to recognize that hypothyroidism is a graded phenomenon and there are wide between-subject differences in overall cardiovascular risk such that subject selection is likely to account for the variability among studies.



Subclinical Thyroid Disease Consensus Panel

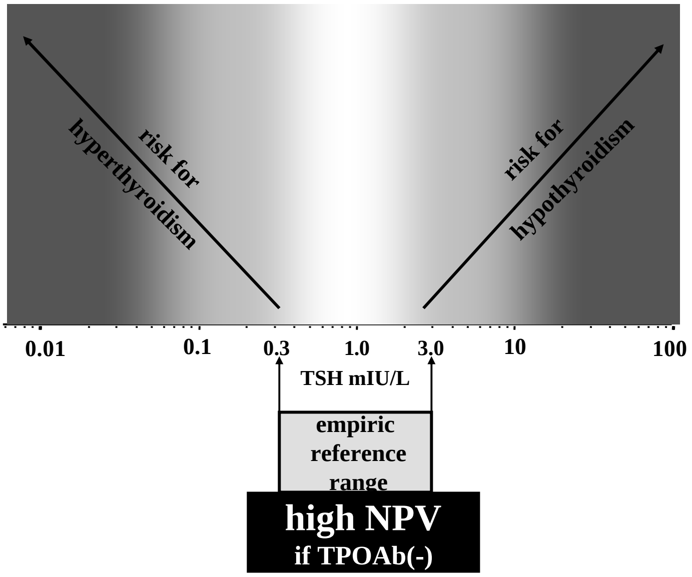
“There is no single level of serum TSH at which clinical action is always either indicated or contraindicated. The higher the TSH the more compelling is the rationale for treatment”.

“It is important to consider the individual clinical context (e.g. pregnancy, lipid profile, TPO antibodies)”.

Surks et al JAMA 291:228, 2004

Even the subclinical thyroid disease consensus panel recognized that we need to be less rigid with respect to our use of the TSH reference range by stating that “ there is no single level of serum TSH at which clinical action is always either indicated or contraindicated. The higher the TSH the more compelling is the rationale for treatment and that it is important to consider the individual’s context such as pregnancy, lipid profile and the presence of TPO antibodies”.

Patients with TSH Outside the Empiric Reference Range Do Not Necessarily Need Treatment!



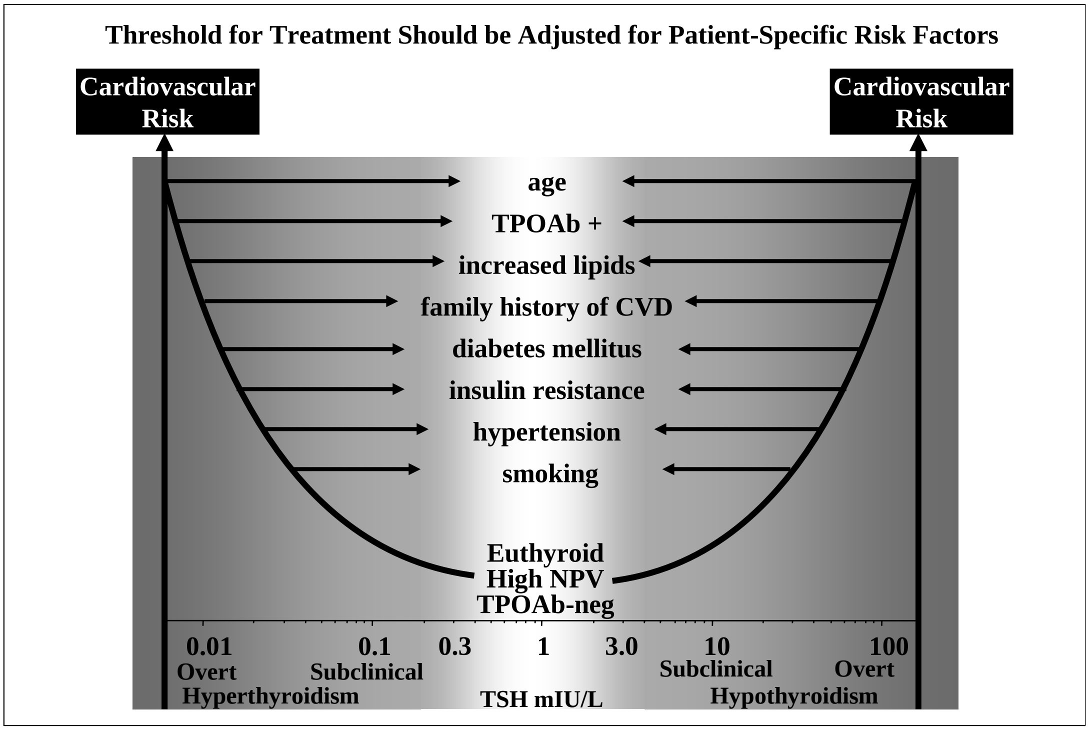
empiric reference range

high NPV
if TPOAb(-)

An empiric range of 0.3 to 3.0 mIU/L would have a high negative predictive value (provided that TPOAb were negative).

The degree of TSH abnormality outside this range would be viewed as a risk factor for current or future development of hyper- or hypothyroidism.

However, patients with TSH outside the empiric reference range would not necessarily need treatment.



Threshold for Treatment Should be Adjusted for Patient-Specific Risk Factors

Cardiovascular Risk

Cardiovascular Risk

age

TPOAb +

increased lipids

family history of CVD

diabetes mellitus

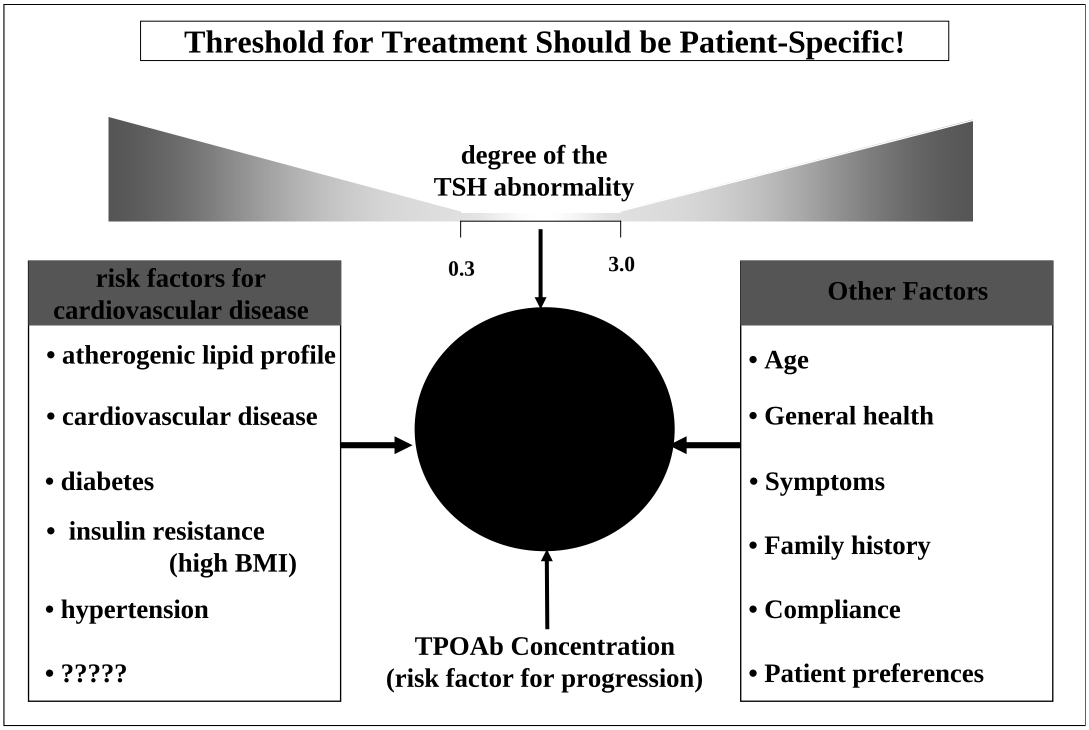
insulin resistance

hypertension

smoking

Euthyroid
High NPV
TPOAb-neg

The threshold for treatment would be adjusted for patient-specific factors for cardiovascular risk such as age, TPOAb positivity, increased lipids, a family history of cardiovascular disease, diabetes, insulin resistance (perhaps BMI as a marker), hypertension and smoking etc.



Threshold for Treatment Should be Patient-Specific!

degree of the TSH abnormality

0.3

3.0

risk factors for cardiovascular disease

- atherogenic lipid profile
- cardiovascular disease
- diabetes
- insulin resistance (high BMI)
- hypertension
- ?????

Other Factors

- Age
- General health
- Symptoms
- Family history
- Compliance
- Patient preferences

TPOAb Concentration (risk factor for progression)

The patient-specific threshold for treatment would be multifactorial and would relate to the degree of TSH abnormality , the TPOAb concentration (because the higher the TPOAb the more rapid the progression of disease) and risk factors for cardiovascular disease and other patient specific factors, including presenting symptoms.

Conclusions

- **Each individual has their own TSH range that spans ~ 0.75 mIU/L. The population reference range is NOT an individual’s ‘normal range’**
- **95% of individuals in a population free of thyroid disease have TSH in the 0.3 to 2.5 mIU/L range.**
- **New Guidelines recommend that pregnant patients should have TSH below 2.5 mIU/L - this is critical in the 1st. trimester.**
- **There is growing data suggesting that mild subclinical hypothyroidism (TSH 3-10 mIU/L) can exaccerbate the risk for cardiovascular disease in susceptible individuals.**
- **The presence of TPOAb increases the risk of progression to overt disease.**

Conclusions - Therapy

- **TSH is a labile hormone and any TSH abnormality should be confirmed before initiating therapy.**
- **There is no TSH level that either indicates or contraindicates the need for L-T4 therapy, although the higher the TSH the more compelling is the rationale to treat with L-T4.**
- **The threshold TSH for initiating therapy should be patient specific.**
- **The threshold for initiating therapy should be lower for patients with a history of cardiovascular disease, older patients, elevated lipids, hypertension, diabetes or planning pregnancy.**